

A PROCESS FOR THE PREPARATION OF C-4 CARBONATE TAXANES**RELATED APPLICATION**

This is division of application Ser. No. 09/712,352, filed on November 14,
5 2000, which claims the priority of US Provisional application No. 60/179,965, filed
on February 3, 2000.

FIELD OF THE INVENTION

The present invention concerns antitumor compounds. More particularly,
10 the invention provides novel orally active paclitaxel derivatives, pharmaceutical
formulations thereof, and their use as oral antitumor agents.

BACKGROUND ART

Paclitaxel is a natural product extracted from the bark of Pacific yew trees,
15 *Taxus brevifolia* and the active constituent of the anticancer agent TAXOL®. It
has been shown to have excellent antitumor activity in *in vivo* animal models, and
recent studies have elucidated its unique mode of action, which involves abnormal
polymerization of tubulin and disruption of mitosis. It is used clinically against a
20 number of human cancers. It is an important cancer agent both therapeutically and
commercially. Numerous clinical trials are in progress to expand and increase the
utility of this agent for the treatment of human proliferative diseases. The results
of TAXOL® clinical studies have been reviewed by numerous authors. A very
recent compilation of articles by a number of different authors is contained in the
entire issue of Seminars in Oncology 1999, 26 (1, Suppl 2). Other examples are
25 such as by Rowinsky et al. in TAXOL®: A Novel Investigational Antimicrotubule
Agent, J. Natl. Cancer Inst., 82: pp 1247-1259, 1990; by Rowinsky and
Donehower in "The Clinical Pharmacology and Use of Antimicrotubule Agents in
Cancer Chemotherapy," Pharmac. Ther., 52:35-84, 1991; by Spencer and
Faulds in "Paclitaxel, A Review of its Pharmacodynamic and Pharmacokinetic
30 Properties and Therapeutic Potential in the Treatment of Cancer," Drugs, 48 (5)
794-847, 1994; by K.C. Nicolaou et al. in "Chemistry and Biology of TAXOL®,"
Angew. Chem., Int. Ed. Engl., 33: 15-44, 1994; by F.A. Holmes, A.P. Kudelka,
J.J. Kavanaugh, M. H. Huber, J. A. Ajani, V. Valero in the book "Taxane

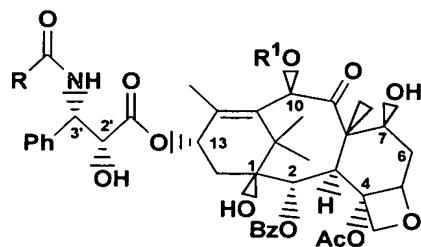


23914

PATENT TRADEMARK OFFICE

Anticancer Agents Basic Science and Current Status" edited by Gunda I. Georg, Thomas T. Chen, Iwao Ojima, and Dolotrai M. Vyas, 1995, American Chemical Society, Washington, DC, 31-57; by Susan G. Arbuck and Barbara Blaylock in the book " TAXOL® Science and Applications" edited by Mathew Suffness, 1995, 5 CRC Press Inc. , Boca Raton, Florida, 379-416; and also in the references cited therein.

A semi-synthetic analog of paclitaxel named docetaxel has also been found to have good antitumor activity and is the active ingredient of the commercially available cancer agent TAXOTERE®. See, Biologically Active Taxol Analogues 10 with Deleted A-Ring Side Chain Substituents and Variable C-2' Configurations, J. Med. Chem., 34, pp 1176-1184 (1991); Relationships between the Structure of Taxol Analogues and Their Antimitotic Activity, J. Med. Chem., 34, pp 992-998 (1991). A review of the clinical activity of TAXOTERE® by Jorge E. Cortes and Richard Pazdur has appeared in Journal of Clinical Oncology 1995, 13(10), 2643 15 to 2655. The structures of paclitaxel and docetaxel are shown below along with the conventional numbering system for molecules belonging to the class; such numbering system is also employed in this application.



20

paclitaxel (TAXOL®): R = Ph; R' = acetyl

docetaxel (TAXOTERE®): R = t-butoxy; R' = hydrogen

Ample evidence that paclitaxel has no oral activity can be found within the 25 following quote from PCT patent application WO98/53811 by inventors Samuel Broder, Kenneth L. Duchin and Sami Selim and the references cited within the quote, which says: "Paclitaxel is very poorly absorbed when administered orally (less than 1%); see Eiseman et. al., Second NCI Workshop on Taxol and Taxus (Sept. 1992); Suffness et.al. in TAXOL Science and Applications (CRC Press 1995). Eisemann et.

al. indicate that paclitaxel has a bioavailability of 0% upon oral administration and Suffness et. al. report that oral dosing with paclitaxel did not seem possible since no evidence of antitumor activity was found on oral administration up to 160 mg mg/kg/day. Moreover, no effective method has been developed to enable the effective 5 administration of oral paclitaxel (ie. a method of increasing the oral bioavailability of paclitaxel) or of other oral taxanes or paclitaxel analogs such as docetaxel which exhibit antitumor activity. For this reason, paclitaxel has not until now been administered orally to human patients, and certainly not in the course of treating paclitaxel-responsive diseases." Another report by J. Terwogt et. al. from The 10 Lancet, July 25th 1998, vol 352 page 285 also describes the low bioavailability of paclitaxel after oral dosing. In our own work, we have orally dosed paclitaxel to doses as high as 160mg/kg/inj in murine (mouse) tumor models (sc M109) without signs of any efficacy and have concluded, like Suffness, that further dosing would not provide efficacy even though toxic doses were not reached. Furthermore, our own 15 attempts to demonstrate activity for orally administered paclitaxel against human tumor xenografts implanted in either athymic mice or athymic rats have to date been unsuccessful.

The intention of this invention is to describe C-4 methyl carbonate taxane 20 analogs which have surprising oral activity and thus would have utility against proliferative diseases after oral administration. Some of the background art pertaining to this invention are shown below.

Certain taxane derivatives with modifications at the C-4 hydroxy group have been described in the art.

U.S. Patent 5,808,102 to Poss et al and PCT published patent application 25 WO 94/14787 contain descriptions of taxane analogs with modifications at the C-4 positions.

Gunda I. Georg et.al describe the synthesis of a C-4 ester analog in *Tetrahedron Letters*, 1994, 35(48) 8931-8934.

S. Chen et. al. describe the synthesis of a C-4 cyclopropyl ester analog in 30 *Journal of Organic Chemistry* 1994, 59(21), 6156-8.

U.S. Patent 5,840,929 to Chen, Shu-Hui covering the C4 methoxy ether derivatives has issued on November 24, 1998. A publication on the same topic has appeared:

Chen, Shu-Hui. First syntheses of C-4 methyl ether paclitaxel analogs and the unexpected reactivity of 4-deacetyl-4-methyl ether baccatin III. *Tetrahedron Lett.* 1996, 37(23), 3935-3938.

- The following reference discusses a number of C-4 ester or carbonate analogs:
- Chen, Shu-Hui; Wei, Jian-Mei; Long, Byron H.; Fairchild, Craig A.; Carboni, Joan; Mamber, Steven W.; Rose, William C.; Johnston, Kathy; Casazza, Anna M.; et al.
- 10 Novel C-4 paclitaxel (Taxol) analogs: potent antitumor agents. *Bioorg. Med. Chem. Lett.* 1995, 5(22), 2741-6.

The preparation of C-4 aziridinyl carbamate analogs has been described in:

Chen, Shu-Hui; Fairchild, Craig; Long, Byron H. Synthesis and Biological Evaluation of Novel C-4 Aziridine-Bearing Paclitaxel (Taxol) Analogs. *J. Med. Chem.* 1995, 38(12), 2263-7.

The following papers describe reactions or transformations which are described as of potential for c-4 analog preparation:

A new method to modify the C-4 position of 10-deacetylbaccatin III. Uoto, Kouichi; Takenoshita, Haruhiro; Ishiyama, Takashi; Terasawa, Hirofumi; Soga, 20 Tsunehiko. *Chem. Pharm. Bull.* 1997, 45(12), 2093-2095.

Samaranayake, Gagini; Neidigh, Kurt A.; Kingston, David G. I. Modified taxols, 8. Deacylation and reacylation of baccatin III. *J. Nat. Prod.* 1993, 56(6), 884-98.

Datta, Apurba; Jayasinghe, Lalith R.; Georg, Gunda I.. 4-Deacetyltaxol and 25 10-Acetyl-4-deacetyltaxotere: Synthesis and Biological Evaluation. *J. Med. Chem.* 1994, 37(24), 4258-60.

In spite of the abovementioned examples of C-4 analogs or methodology to prepare them, no evidence of orally active C-4 analogs has been supplied. Both TAXOL® and TAXOTERE® have no oral activity in human or animal models as 30 mentioned in the following prior art described below on taxanes and oral modulators. Thus, the art to date does not suggest that C-4 taxanes should be different than other taxanes and therefore they should not be orally active. To the best of our knowledge, the art in no way specifically identifies any C-4 analogs which may have oral utility.

The invention described in this patent application identifies novel C-4 analogs which due to their unique substitution surprisingly have oral activity.

The following references describe methods or possible methods for orally active taxanes.

5 Methods for administering taxanes in the presence of modulators have been reported to increase the amount of taxanes in the plasma after oral administration: Terwogt, Jetske M. Meerum; Beijnen, Jos H.; Ten Bokkel Huinink, Wim W.; Rosing, Hilde; Schellens, Jan H. M. Coadministration of cyclosporin enables oral therapy with paclitaxel. Lancet (1998), 352(9124), 285.

10 Terwogt, Jetske M. Meerum; Malingre, Mirte M.; Beijnen, Jos H.; Huinink, Wim W. ten Bokkel; Rosing, Hilde; Koopman, Franciska J.; Van Tellingen, Olaf; Swart, Martha; Schellens, Jan H. M. Coadministration of oral cyclosporin A enables oral therapy with paclitaxel. Clin. Cancer Res. (1999), 5(11), 3379-3384.

15 Hansel, Steven B. A method of making taxanes orally bioavailable by coadministration with cinchonine. PCT Int. Appl. WO 9727855 published August 7, 1997.

Broder, Samuel; Duchin, Kenneth L.; Selim, Sami. Method and compositions for administering taxanes orally to human patients using a cyclosporin to enhance bioavailability. PCT Int. Appl. WO 9853811 published December 3, 1998.

20 These reports contain no antitumor efficacy data but the presence of taxanes in the plasma is extrapolated to show their potential for anticancer utility.

At least one report of oral activity of prodrugs in preclinical animal models has appeared in the prior art: Scola, Paul M.; Kadow, John F.; Vyas, Dolatrai M. Preparation of paclitaxel prodrug derivatives. Eur. Pat. Appl. EP 747385 published December 11, 1996. The oral bioavailability of the prodrug which had oral efficacy was not disclosed and no further reports of these compounds progressing to man have appeared.

Very recently, an abstract describing a taxane analog (IDN-5109) with oral activity against tumors in mice was disclosed at the American Association of Cancer Researchers in Philadelphia in 1999. The reference for the abstract is: Pratesi G, Polizzi D, Totoreto M, Riva A, Bombardelli E, Zunino F : IDN5109 a new taxane active after oral administration. Proc Am Assoc Cancer Res 1999 40 Abs 1905, Istituto Nazionale Tumori, 20133 Milan and Indena SpA, 20139, Milan, Italy. The

structure of this compound is quite different than compounds described in the present invention. Unlike the compounds encompassed by the present invention, IDN-5109 is derived from 14-betahydroxy baccatin III and has an acetate on the hydroxy group at the C-4 position.

- 5 Two references on the iv activity of this compound are included for completeness.

Nicoletti ML, Rossi C, Monardo C, Stura S, Morazzoni P, Bombardelli E, Valoti G, Giavazzi R.: Antitumor efficacy of a paclitaxel analogue, IDN5109, on human ovarian carcinoma xenografts with different sensitivity to paclitaxel. Proc Am
10 Assoc Cancer Res 1999 40 Abs 1910 [Evals+citations].

Polizzi, Donatella; Pratesi, Graziella; Tortoreto, Monica; Supino, Rosanna; Riva, Antonella; Bombardelli, Ezio; Zunino, Franco. A novel taxane with improved tolerability and therapeutic activity in a panel of human tumor xenografts. *Cancer Res.* 1999, 59(5), 1036-1040.

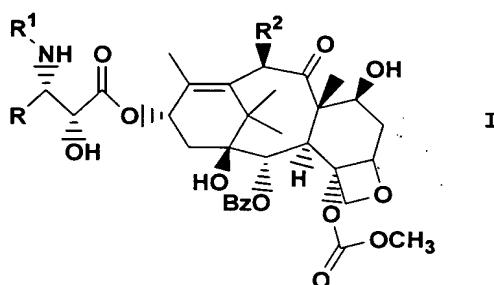
- 15 Paclitaxel is a highly schedule dependent drug that benefits traditionally from prolonged tumor exposure times. This relates to paclitaxel's mechanism of action as taxanes only recognize and bind to the polymerized state of tubulin which occurs only during a brief period of the cancer cell cycle. The currently used intravenous infusions (1-3 hours) are now readily accepted and efficacious and preclude the routine use of protracted (>24 hours) continuous schedules. However, an oral taxane may provide a compliant and cost effective way of accomplishing such extended duration of exposure. Recently, clinical utility has also been demonstrated using repetitive once weekly administrations of moderate (i.e., other than maximally tolerated) doses of TAXOL® and an oral taxane would be ideal for such protracted regimens. Other purported clinical indications for taxanes use (e.g., rheumatoid arthritis, multiple sclerosis) would also benefit from the availability of an oral taxane. An orally administered effective taxane would offer both an attractive alternative from the parenteral format of current clinical taxane usage, and a potential therapeutic advantage because of the many avenues of scheduling yet to be investigated.

Thus it is clear there is a great need to identify taxanes with both good oral bioavailability and good oral efficacy, which are comparable to paclitaxel administered parenterally.

5

SUMMARY OF INVENTION

This invention relates to novel antitumor compounds represented by formula I, or pharmaceutically acceptable salts thereof:



10

wherein:

R is phenyl, isopropyl, or tert butyl;

15 R¹ is -C(O)R^Z in which R^Z is (CH₃)₃CO-, (CH₃)₃CCH₂-, CH₃(CH₂)₃O-, cyclobutyl-, cyclohexyloxy, or (2-furyl);

R² is CH₃C(O)O-.

20 Another aspect of the present invention provides a method for inhibiting tumor growth in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula I, or its pharmaceutically acceptable salts. Preferably, the method of administration is oral.

25

Yet, another aspect of the present invention provides a pharmaceutical formulation which comprises an antitumor effective amount of a compound of

formula I, or its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants.

5

DETAILED DESCRIPTION OF THE INVENTION

In this disclosure of the invention, unless otherwise specified explicitly or in context, the following definitions apply. In this application, the symbols once defined retain the same meaning throughout the application, until they are redefined.

- 10 The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C₁₋₆ alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C₁₋₆ alkyl" 15 can also refer to C₁₋₆ alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C₂₋₆ alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, 20 "C₂₋₆ alkenyl" can also refer to C₂₋₆ alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C₂₋₆ alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl. As used herein t-butyloxy and t-butoxy are 25 used interchangeably.

- "Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl independently substituted with one to five (but preferably one to three) groups selected from C₁₋₆ alkanoyloxy, hydroxy, halogen, C₁₋₆ alkyl, trifluoromethyl, C₁₋₆ alkoxy, aryl, C₂₋₆ 30 alkenyl, C₁₋₆ alkanoyl, nitro, amino, cyano, azido, C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen.

Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl,

- 5 tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Hydroxy protecting groups" include, but are not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, 1-methyl-1-methoxyethyl, tetrahydropyranyl,

- 10 tetrahydrothiopyranyl, dialkylsilyl ethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyldimethylsilyl ether, dialkyl alkoxy silyl ethers such as diisopropyl methoxy silyl ethers; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as 15 methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl. Additional examples of hydroxy protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., 1999, John Wiley & Sons, New York.

"Ph" means phenyl; "ipr" means isopropyl;

20 The substituents of the substituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups and moieties described herein, may be alkyl, alkenyl, alkynyl, aryl, heteroaryl and/or may contain nitrogen, oxygen, sulfur, halogens and include, for example, lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, nitro, amino, and keto.

- 25 A preferred embodiment are compounds I, or pharmaceutically acceptable salts thereof which are depicted in Table I below.

Table I**Orally Active C-4 Methyl Carbonate Taxanes**

Compound	R	R¹	R²
Ia	(CH ₃) ₃ C-	(CH ₃) ₃ COC(O)-	CH ₃ C(O)O-
Ib	(CH ₃) ₂ CH-	(CH ₃) ₃ COC(O)-	CH ₃ C(O)O-
Ic	Phenyl-	(CH ₃) ₃ CCH ₂ C(O)-	CH ₃ C(O)O-
Id	Phenyl-	CyclobutylC(O)-	CH ₃ C(O)O-
Ie	(CH ₃) ₃ C-	CyclohexylOC(O)-	CH ₃ C(O)O-
If	(CH ₃) ₃ C-	(CH ₃) ₃ CCH ₂ C(O)-	CH ₃ C(O)O-
Ig	Phenyl-	(CH ₃) ₃ COC(O)-	CH ₃ C(O)O-
Ih	Phenyl-	CH ₃ (CH ₂) ₃ OC(O)-	CH ₃ C(O)O-
Ij	(CH ₃) ₃ C-	CyclobutylC(O)-	CH ₃ C(O)O-
Ik	(CH ₃) ₃ C-	(2-furyl)C(O)-	CH ₃ C(O)O-

An even more preferred embodiment are compounds I, or pharmaceutically acceptable salts thereof which are shown in Table II.

Table II

Compound	R	R¹	R²
Ia	(CH ₃) ₃ C-	(CH ₃) ₃ COC(O)-	CH ₃ C(O)O-
If	(CH ₃) ₃ C-	(CH ₃) ₃ CCH ₂ C(O)-	CH ₃ C(O)O-
Ij	(CH ₃) ₃ C-	CyclobutylC(O)-	CH ₃ C(O)O-
Ik	(CH ₃) ₃ C-	(2-furyl)C(O)-	CH ₃ C(O)O-

The new compounds that have the general formula I display a significant inhibitory effect with regard to abnormal cell proliferation, and have therapeutic properties that make it possible to treat patients who have pathological conditions associated with an abnormal cell proliferation. In addition, these compounds possess

significant oral bioavailability and thus can elicit their positive therapeutic effects after being administered orally.

The pathological conditions include the abnormal cellular proliferation of malignant or non-malignant cells in various tissues and/or organs, including, non-limitatively, muscle, bone and/or conjunctive tissues; the skin, brain, lungs and sexual organs; the lymphatic and/or renal system; mammary cells and/or blood cells; the liver, digestive system, and pancreas; and the thyroid and/or adrenal glands. These pathological conditions can also include psoriasis; solid tumors; ovarian, breast, brain, prostate, colon, stomach, kidney, and/or testicular cancer, Karposi's sarcoma; 5 cholangiocarcinoma; choriocarcinoma; neuroblastoma; Wilm's tumor, Hodgkin's disease; melanomas; multiple myelomas; chronic lymphocytic leukemias; and acute or 10 chronic granulocytic lymphomas.

The novel compounds in accordance with the invention are particularly useful in the treatment of non-Hodgkin's lymphoma, multiple myeloma, melanoma, and 15 ovarian, urothelial, oesophageal, lung, and breast cancers. The compounds can be utilized to prevent or delay the appearance or reappearance, or to treat these pathological conditions. The compounds may be used as antiangiogenesis inhibitors for both anticancer activities or for abnormal wound healing or other 20 hyperproliferative diseases dependent on blood vessel formation.

In addition, the compounds of formula I are useful in treating and/or preventing polycystic kidney diseases (PKD) and rheumatoid arthritis. The 25 compounds of this invention may also be useful for the treatment of Alzheimer's or Parkinson's disease or multiple sclerosis. While some of the products of general formula I are of interest due to advantages over commercial taxanes following iv administration, their main attribute is due to their unique properties after oral administration.

The compounds of this invention can be made by techniques from the conventional organic chemistry repertoire. Schemes 1-3, which depict processes that 30 compounds within the scope of formula I can be made, are only shown for the purpose of illustration and are not to be construed as limiting the processes to make the compounds by any other methods.

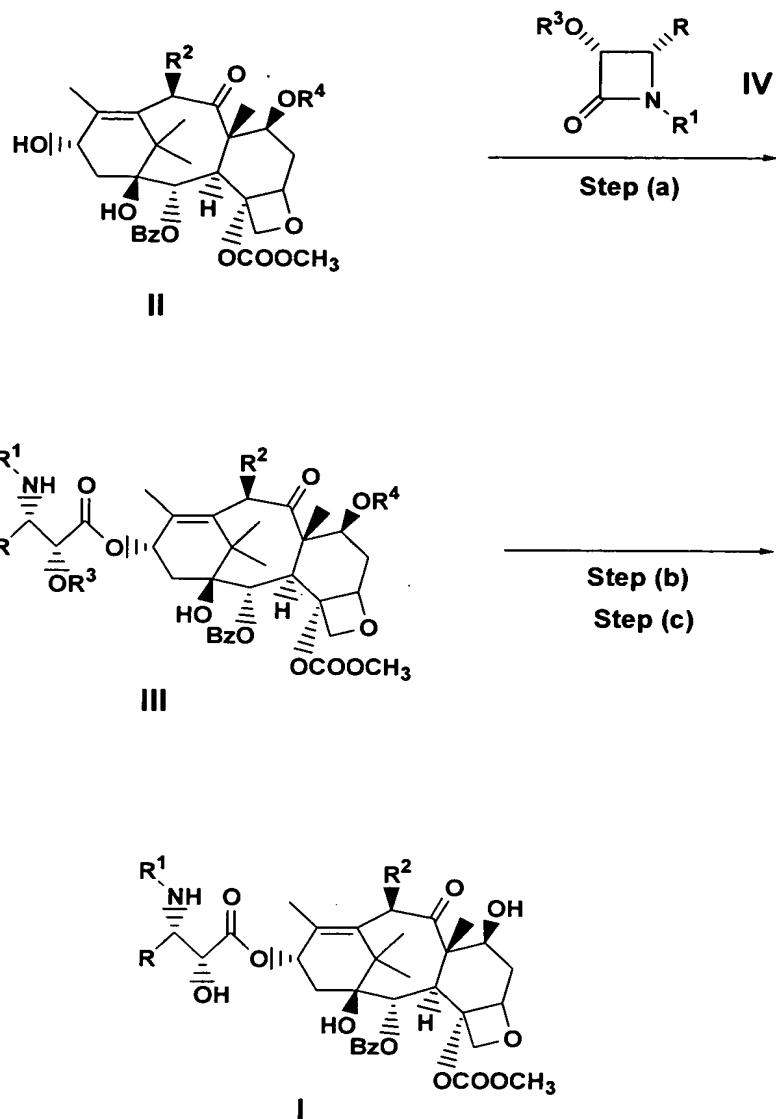
A compound of formula I may be produced by the processes as depicted in Schemes 1-3 which follow. The methods can be readily adapted to variations in order to produce compounds within the scope of formula I but not specifically disclosed. Further variations of the methods to produce the same compounds in 5 somewhat different fashion will also be evident to one skilled in the art. The numbering on baccatin III derivative of formula II as used in this application is as shown in the initial taxane structure.

One of the ways the compounds of this invention can be made is by the general method which shown is Scheme 1. In Step (a) of the scheme, azetidinone IV 10 is reacted with a compound of formula II (a baccatin III derivative). The general class of azetidinones (β -lactams) of formula IV are well known. Methods for preparing suitably substituted β -lactams can be found in U.S. patent 5,175,315, European patent application 0 590 267 A2, the other U.S. patents or literature mentioned above, or references therein by Ojima et al. in Tetrahedron, 48, No. 34, pp 6985-7012 (1992); 15 Journal of Organic Chemistry, 56, pp 1681-1683 (1991); and Tetrahedron Letters, 33, No. 39, pp 5737-5740 (1992); by Brieva et al. in J. Org. Chem., 58, pp 1068-1075; by Palomo et al. in Tetrahedron Letters, 31, No. 44, pp 6429-6432 (1990); and in Rey, Allan W.; Droghini, Robert; Douglas, James L.; Vemishetti, Purushotham; Boettger, Susan D.; Racha, Saibaba; Dillon, John L. Can. J. Chem. 72(10), 2131-6 (1994).

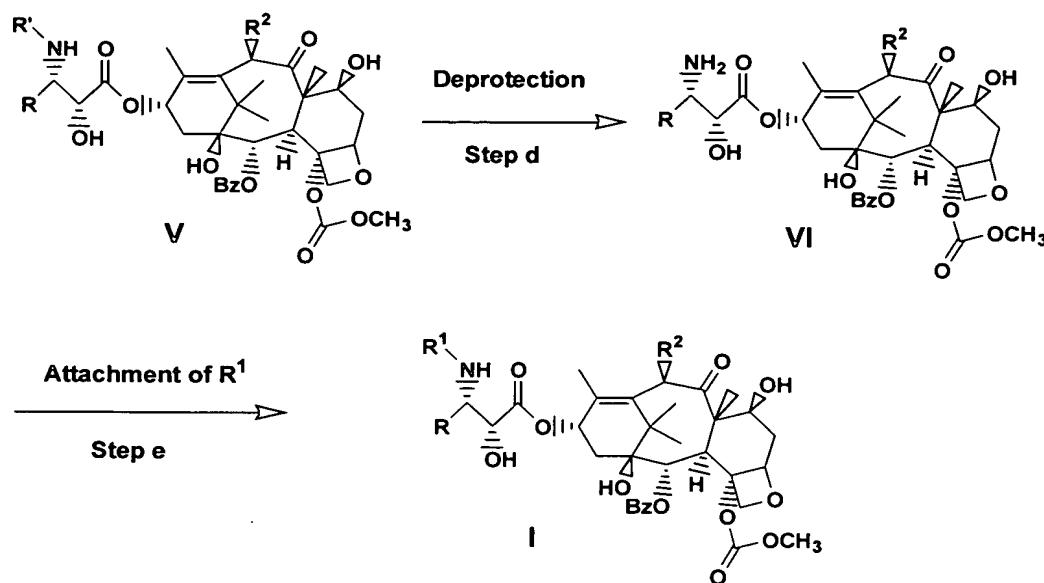
20 All disclosures are herein incorporated by reference in their entirety. The methods that can be adapted to variations in order to produce other azetidinones within the scope of formula IV, but not specifically disclosed herein or in the above references or reported elsewhere, will be obvious to anyone skilled in the art.

25 The baccatin III derivatives (II) can be attached to a sidechain using any of the methodology which is now already well known in the art. The many references cited in this invention disclosure and Tetrahedron, 48, No. 34, pp 6985-7012 (1992) describe processes whereby the class of azetidinones of formula IV are reacted with (C)13-hydroxy group of baccatin III derivatives or metal alkoxide thereof to afford 30 taxane analogues with a variety of (C)13-side chains. In Step (a) of Scheme 1, it is advantageous to convert the hydroxy group on the (C)13-carbon into a metal alkoxide before the coupling. The formation of a desired metal alkoxide may be done by reacting a compound of formula II with a strong metal base, such as lithium

- diisopropylamide, C1-6 alkylolithium, lithium or sodium or potassium bis(trimethylsilyl)amide, phenyllithium, sodium hydride, potassium hydride, lithium hydride, or the like base. For example when lithium alkoxide is desired, a compound of formula II may be reacted with n-butyllithium in an inert solvent such as
- 5 tetrahydrofuran. For examples of attachment of substituted baccatins with a suitably substituted lactam via the method of Holton see U.S. 5,175,315; U.S. 5,466,834; U.S. 5,229,526; U.S. 5,274,124; U.S. 5,243,045; U.S. 5,227,400; U.S. 5,336,785, and U.S. patent 5,254,580, U.S. 5,294,637, or EP 0 590 267 A2. Some examples of using β -lactams to prepare other substituted taxane derivatives are in PCT WO94/14787.
- 10 This patent also describes an alternative method for attaching substituted isoserine sidechains to substituted baccatins which would be applicable for the compounds of this invention. This same alternate method is described in another publication by Kingston et. al. Tetrahedron Lett. (1994), 35(26), 4483-4. Further information on alternative methods to attach sidechains to baccatins are contained in Thottathil, et.al
- 15 Eur. Pat. Appl. EP 735036 published 10/2/96.

Scheme 1

Scheme 2



As used herein, R³ and R⁴ are conventional hydroxy protecting groups.

Conventional hydroxy protecting groups are moieties which can be employed to block or protect a hydroxy function, and they are well known to those skilled in the art.

- 5 Preferably, said groups are those which can be removed by methods which result in no appreciable destruction to the remaining portion of the molecule. Examples of such readily removable hydroxy protecting groups include chloroacetyl, methoxymethyl, 1-methyl-1-methoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, dialkylsilyl ethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether,

10 triethylsilyl ether, and t-butyldimethylsilyl ether, dialkyl alkoxy silyl ethers such as diisopropyl methoxy silyl ethers; 2,2,2-trichloroethoxymethyl, 2,2,2-trichloroethyloxycarbonyl (or simply trichloroethyloxycarbonyl), benyloxycarbonyl and the like. Other suitable hydroxy protecting groups which may be used are found in Chapter 2 of "Protecting Groups in Organic Synthesis", Third Ed., by Theodora W.

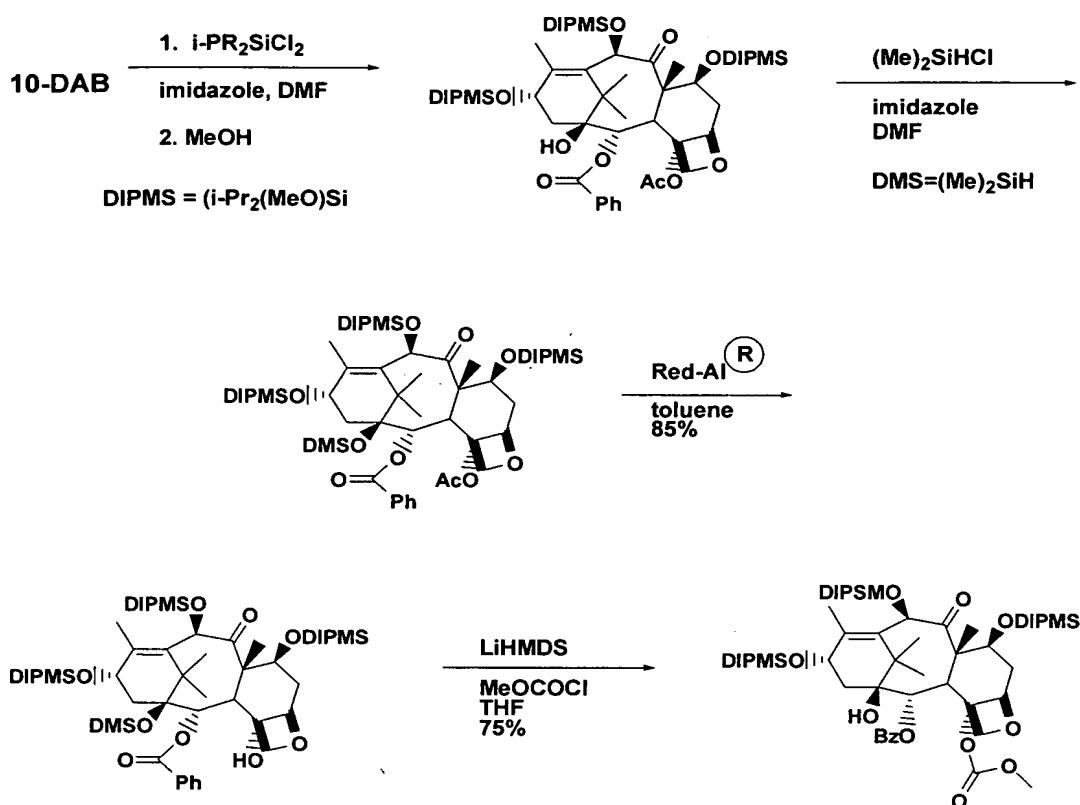
15 Greene and Peter G.M. Wuts (1999, John Wiley & Sons, New York). A protecting group for formula IV compounds which has been used frequently in the literature is trialkylsilyl. Most preferred groups for R³ include 1-methyl-1-methoxyethyl (MOP), a trialkyl silyl ether, or a dialkyl alkoxy silyl ether such as a diisopropyl methoxy silyl ether. The most preferred group for R⁴ is a dialkyl alkoxy silyl ether such as a

20 diisopropyl methoxy silyl ether but a trialkyl silyl ether or a carbonate such as a benzyl

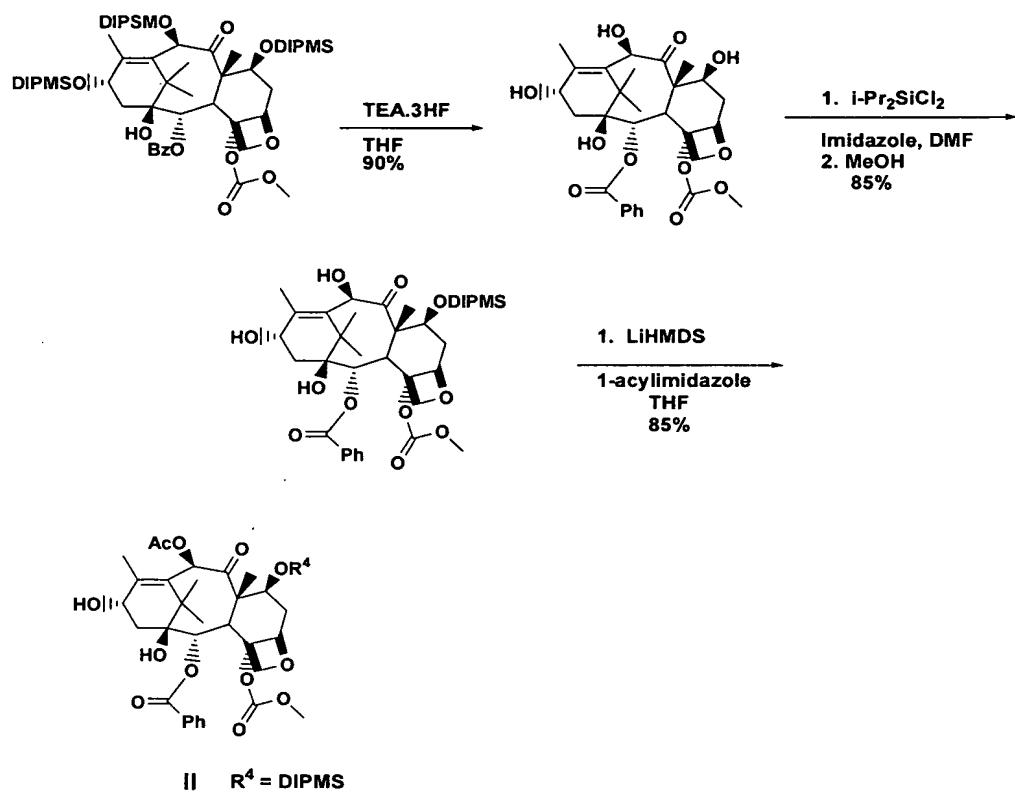
carbonate might also be preferred. In Step (b), the protecting group R³ or R⁴ or possibly both are removed. If R³ or R⁴ are silyl based protecting groups, removal is effected by triethylamine trihydrofluoride in THF solvent. Other fluoride sources could also be utilized. For example tetrabutyl ammonium fluoride, pyridinium
5 hydrofluoride, potassium fluoride, or cesium fluoride may find utility. The potassium fluoride may be utilized in combination with a complexing agent such as 18-crown-6 or the like to aid in desilylation. A solvent such as acetonitrile is typically used under these conditions. Other conditions such as mild aqueous hydrochloric acid or trifluoroacetic acid and a cosolvent such as acetonitrile or THF may be useful for
10 deprotection of the silyl groups. The same acidic conditions work well to remove the 1-methyl-1-methoxyethyl (MOP) protecting group.

The conditions actually employed will depend on the protecting groups employed for R³ and R⁴. For example one preferred route might employ a MOP group for R³ and a diisopropyl methoxy silyl ether for R⁴. In this case, step b would
15 entail a mild acidic workup using aqueous hydrochloric acid and an organic solvent. The resulting 2' deprotected compound would be exposed to a fluoride source such as triethylamine trihydrofluoride in THF solvent in step c to produce compound I after chromatographic or crystallographic purification.

Scheme 3
Preferred Synthesis of Protected C-4 Methyl Carbonate Baccatin



Scheme 3 continued



Another aspect of the invention involves the synthesis of compounds I with novel substituents R² at the C-10 position. These compounds can be prepared by attaching an alternative ester rather than the acetate ester group which is attached in Scheme 3.

5 An alternative preparation of compounds I is depicted in Scheme 2. It involves the conversion of one compound V in which R' forms a nitrogen protecting group such as tBuO(CO)- (tBoc) or PhCH₂OC(O)- (CBZ). The groups can be removed by acidic hydrolysis or in the case of CBZ by hydrogenolysis. The preparation of the amine intermediate VI is described in the examples and is carried
10 out by methodology which is well known in the art. The amine intermediate VI is dissolved in an inert solvent such as ethyl acetate and a base such as sodium bicarbonate is added. A stoichiometric or slightly greater amount of most preferably an acid chloride, (i.e., R¹-C(O)Cl) chloroformate or, alternatively, acid anhydride is added to provide compound I directly.

15 The preparation of the baccatin derivatives of structure II (as shown in Scheme 1 where R² is AcO-) is shown in Scheme 3 and illustrated in Preparation 7. The specific examples that follow illustrate the syntheses of the compounds of the instant invention, and are not to be construed as limiting the invention in sphere or scope. The method may be adapted to variations in order to produce the
20 compound embraced by this invention but not specifically disclosed. Further, variations of the methods to produce the same compound in a somewhat different manner will also be evident to one skilled in the art.

In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR)
25 spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs or br s), broad doublet (bd or br d), broad triplet (bt or br t), broad quartet (bq or br q), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d6 (deuterated acetone), DMSO-d6 (perdeuteriodimethylsulfoxide), D2O
30

(deuterated water), CDCl₃ (deuterochloroform) and other conventional deuterated solvents. The infrared (IR) spectral description include only absorption wave numbers (cm⁻¹) having functional group identification value.

Celite is a registered trademark of the Johns-Manville Products Corporation
5 for diatomaceous earth.

Silica gel used in the following experimentals is silica gel 60 with a particle size 230-400 mesh obtained from EM Separations Technology.

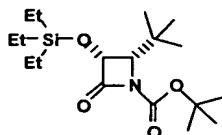
The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: DAB (deacetyl baccatin III); MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); v/v (volume/volume); FAB (fast atom bombardment); NOBA (m-nitrobenzyl alcohol); min (minute(s)); h or hr(s) (hour(s)); DCC (1,3-dicyclohexylcarbodiimide); BOC (t-butoxycarbonyl); CBZ or Cbz (benzyloxycarbonyl); Bn (benzyl); Bz (benzoyl); Troc (2,2,2-trichloroethyloxycarbonyl), DMS (dimethylsilyl), TBAF (tetrabutylammonium fluoride), DMAP (4-dimethylaminopyridine); TES (triethylsilyl); DMSO (dimethylsulfoxide); THF (tetrahydrofuran); HMDS (hexamethyldisilazane); MeOTf (methyltriflate); NMO (morpholine-N-oxide); (DHQ)₂PHAL (hydroquinine 1,4-phthalazinediyl diether). Tf = triflate
20 =trifluoromethanesulfonate; LRMS (low resolution mass spectrometry); ESI (electrospray ionization); TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical); DBU (diazobicycloundecene); MOMCl (chloromethyl methyl ether); Ac (acetyl); (Ar, aryl); Bz (benzoyl); Cbz (benzyloxycarbonyl); DCI (desorption chemical ionization); DMF (dimethylformamide); FAB (fast atom bombardment);
25 H (hour(s)); HRMS (high resolution mass spectrometry); LiHMDS (lithium hexamethyldisilazane or lithium bis(trimethylsilyl)amide); HMDS (hexamethyldisilazane); i-PrOH (isopropylalcohol); min (minute(s)); MS (mass spectrometry); Ph (phenyl); rt (room temperature); tBu (tertiarybutyl); TES (triethylsilyl), TLC (thin layer chromatography) Y (yield) TPAP (tetrapropyl
30 ammonium peruthenate); MCPBA (meta chloroperoxy benzoic acid); LDA (lithium diisopropyl amide); TBS (tert-butyl-dimethylsilyl); 18-crown-6 (1, 4, 7, 10, 13, 16-hexaoxacyclo-octadecane); DEAD (diethylazodicarboxylate); Red-Al® (Aldrich Catalogue) is 65⁺ weight % solution of sodium bis(2-

methoxyethoxy)aluminum hydride in toluene; DCM means dichloromethane; "sat." means saturated.

Preparations:

5 **Preparation 1**

(\pm)-cis-4-*tert*-Butyl-1-*tert*-butyloxycarbonyl-3-triethylsilyloxy-azetidin-2-one

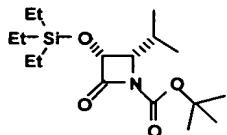


- 10 Trimethylacetaldehyde (20.3 mL, 1.25 equiv) was added to a stirred suspension of *p*-anisidine (18.4 gm, 0.150 mole) and anhydrous Na₂SO₄ (150 gm) in anhydrous DCM (250 mL) at RT. After 2 hr, this was filtered and the solid was washed with additional anhydrous DCM. The solvent was removed from the filtrate and the crystalline residue was dissolved in anhydrous DCM (750 mL) and placed under a nitrogen atmosphere. Triethylamine (48.0 mL, 2.3 equiv) was added and the reaction was cooled to -78 °C. Benzyloxacyetyl chloride (27.2 mL 1.15 equiv) was added dropwise and then the reaction was allowed to warm to RT. After 24 hr, this was washed with 0.5 M HCl (twice), sat. aqueous NaHCO₃ solution, brine and dried (Na₂SO₄). The solvent was removed and the residue was chromatographed on a silica gel column (gradient elution with 20% DCM in hexane containing 0 to 20% EtOAc) to afford (\pm)-cis-4-*tert*-butyl-3-benzyloxy-1-*p*-methoxybenzyl-azetidinone as a crystalline solid (46.9 gm, 92%): ¹H NMR (CDCl₃) δ 1.09 (s, 9H), 3.81 (s, 3H), 4.15 (d, 1H, J=5.5 Hz), 4.77 (d, 1H, J=11.9 Hz), 4.81 (d, 1H, J=5.5 Hz), 5.03 (d, 1H, J=11.9 Hz) 6.87 - 7.43 (m, 9 Hz); LRMS (ESI) 340 ([M+H]⁺). A solution of ceric ammonium nitrate (60.4 gm 3.6 equiv) in 900 mL of water was added to a well stirred solution of the azetidinone (10.38 gm, 30.6 mmole) in acetonitrile (600 mL) in an ice bath over 1 hr. The reaction was then extracted with EtOAc (twice) and the combined organic extracts were washed with sat. aqueous NaHCO₃ solution (twice), 20% aqueous NaHSO₃ solution, sat. aqueous NaHCO₃ solution and brine. After being

dried (Na_2SO_4), the solvents were removed and the residue was chromatographed on a silica gel column (gradient elution with portions of hexane containing 10 to 40% EtOAc) to afford 5.64 gm of slightly impure (\pm) -*cis*-3-benzyloxy-4-*tert*-butyl-azetidin-2-one: ^1H NMR (CDCl_3) δ 1.04 (s, 9H), 3.51 (d, 1H, $J=5.2$ Hz), 4.71 (m, 2H), 4.96 (d, 1H, $J=11.9$ Hz) 6.10 (brs, 1H), 7.35 (m, 5H). A suspension of this material (5.54 gm, 23.8 mmole) and 2.5 gm of 10% Pd on charcoal in absolute EtOH (100 mL) was hydrogenated (34 psi H_2 , Parr apparatus) for 23 hr. A further 2 gm of the Pd catalyst was added and the hydrogenation was continued for a further 17 hr at 50 psi H_2 . The catalyst was removed by filtration and the solvent was removed from the filtrate to leave crude (\pm) -*cis*-3-hydroxy-4-(*tert*-butyl)-azetidin-2-one: ^1H NMR ($\text{CDCl}_3 + 1$ drop D_2O) δ 1.05 (s, 9H), 3.48 (d, 1H, $J=5.0$ Hz), 4.98 (d, 1H, $J=5.0$ Hz). This material was dissolved in dry DMF (40 mL) and imidazole (3.24 gm, 2 equiv) and triethylsilyl chloride (4.0 mL, 1 equiv) were added. After 10 min, the reaction was partitioned between water and a mixture of EtOAc and hexane (1 : 1). The organic phase was washed with water (twice), brine and then dried (Na_2SO_4). The solvents were removed and the residue was chromatographed on a silica gel column (gradient elution with 20 to 25% EtOAc in hexane) to give (\pm) -*cis*-4-*tert*-butyl-3-triethylsilyloxy-azetidin-2-one (3.86 gm): ^1H NMR (CDCl_3) δ 0.70 (m, 6H), 0.98 (m, 18H), 3.39 (d, 1H, $J=5.0$ Hz), 4.88 (dd, 1H, $J = 2.1, 5.0$ Hz), 6.08 (brs, 1H). A solution of this azetidinone (2.04 gm, 7.92 mmole), diisopropylethyl amine (1.66 mL, 1.2 equiv), di-*tert*-butyl dicarbonate (1.90 gm, 1.1 equiv) and *p*-dimethylaminopyridine (194 mg, 0.2 equiv) in dry DCM (24 mL) was left stirring at RT for 3 hr. The reaction was diluted with DCM, washed with brine and dried (Na_2SO_4). Removal of the solvent followed by silica gel column chromatography (gradient elution with 0 to 20% EtOAc in hexane) afforded 2.71 gm (96%) of the title compound as an oil: ^1H NMR (CDCl_3) δ 0.70 (m, 6H), 1.00 (m, 9H), 1.09 (s, 9H), 1.53 (s, 9H), 3.90 (d, 1H, $J = 6.5$ Hz), 4.93 (d, 1H, $J = 6.5$ Hz).

Preparation 2**(\pm)-cis-1-*tert*-butyloxycarbonyl-4-*iso*-propyl-3-triethylsilyloxy-azetidin-2-one**

5



Isobutyraldehyde (4.62 mL, 1.25 equiv) was added to a stirred suspension of *p*-anisidine (5.00 gm, 40.7 mmole) and anhydrous Na₂SO₄ (25 gm) in anhydrous DCM (80 mL) at RT. After 1 hr, this was filtered and the solid was washed with additional anhydrous DCM. The solvent was removed from the filtrate and the residue was dissolved in anhydrous DCM (200 mL) and placed under a nitrogen atmosphere.

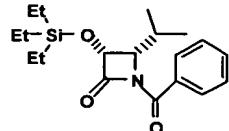
Triethylamine (13.1 mL, 2.3 equiv) was added and the reaction was cooled to -78 °C. Acetoxyacetyl chloride (5.00 mL 1.15 equiv) was added dropwise and the reaction was allowed to warm to RT. After 20 hr, this was washed with 0.5 M HCl (twice), sat. aqueous NaHCO₃ solution, brine and dried (Na₂SO₄), the solvent was removed and the residue was chromatographed on a silica gel column (gradient elution with 20 to 30% EtOAc in hexane) to afford (\pm)-cis-3-acetoxy-4-isopropyl-1-*p*-methoxybenzyl-azetidin-2-one as a solid (7.15 gm, 63%): ¹H NMR (CDCl₃) δ 0.99 (d, 3H, J = 7.0 Hz), 1.02 (d, 3H, J = 7.0 Hz), 2.20 (s, 3H), 3.82 (s, 3H), 4.24 (t, 1H, J=5.6 Hz), 6.06 (d, 1H, J = 5.3 Hz), 6.88 - 7.38 (m, 4H). A solution of ceric ammonium nitrate (51.3 gm 3.6 equiv) in 750 mL of water was added to a well stirred solution of the azetidinone (7.20 gm, 26.0 mmole) in acetonitrile (500 mL) in an ice bath over 1 hr. The reaction was then extracted with EtOAc (twice) and the combined organic extracts were washed with sat. aqueous NaHCO₃ solution (twice), 20% aqueous NaHSO₃ solution, sat. aqueous NaHCO₃ solution and brine. After being dried (Na₂SO₄) the solvents were removed to leave 4.26 gm of crude (+)-cis-3-acetoxy-4-*iso*-propyl-azetidin-2-one: ¹H NMR (CDCl₃) δ 0.86 (d, 3H, J = 6.6 Hz), 0.99 (d, 3H, J = 6.6 Hz), 1.89 (m, 1H), 2.17 (s, 3H), 3.52 (dd, 1H, J = 4.8, 9.0 Hz), 5.96 (dd, 1H, J

= 2.5, 4.6 Hz), 6.38 (br s, 1H), LRMS (negative ESI) 170 [(M-H)⁻]. A suspension of this material (4.26 gm, 24.9 mmole) and K₂CO₃ (102 mg, 0.03 equiv) in MeOH (40 mL) was left stirring at RT for 1.5 hr. Amberlite IR-20 was then added to neutralize the reaction. This was filtered and the solvent was removed from the filtrate to leave 5 crude (+)-cis-3-hydroxy-4-*iso*-propyl-azetidin-2-one. This material was dissolved in dry DMF (40 mL) and imidazole (3.39 gm, 2 equiv) and triethylsilyl chloride (4.19 mL, 1 equiv) were added. After 10 min, the reaction was partitioned between water and a mixture of EtOAc and hexane (1 : 1). The organic phase was washed with water (twice), brine and then dried (Na₂SO₄). The solvents were removed and the 10 residue was chromatographed on a silica gel column (gradient elution with 25 to 35% EtOAc in hexane) to give (\pm)-cis-4-isopropyl-3-triethylsilyloxy-azetidin-2-one (4.63 gm, 77%): ¹H NMR (CDCl₃) δ 0.65 - 1.03 (m, 21H), 1.93 (m, 1H), 3.29 (dd, 1H, J = 4.8, 9.1 Hz), 4.87 (dd, 1H, J = 2.8, 4.7 Hz), 6.05 (br s, 1H). A solution of this azetidinone (1.05 gm, 4.32 mmole), diisopropylethyl amine (0.90 mL, 1.2 equiv), di- 15 *tert*-butyl dicarbonate (1.04 gm, 1.1 equiv) and p-dimethylamino pyridine (106 mg, 0.2 equiv) in dry DCM (10 mL) was left stirring at RT for 30 min. The reaction was diluted with DCM, washed with brine and dried (Na₂SO₄). Removal of the solvent followed by silica gel column chromatography (gradient elution with 10 to 20% EtOAc in hexane) afforded 1.31 gm (88%) of the title compound as an oil: ¹H NMR δ 20 (CDCl₃) 0.66 - 1.07 (m, 21H), 1.53 (s, 9H), 2.15 (m, 1H), 3.87 (t, 1H, J = 6.4 Hz), 4.88 (d, 1H, J = 6.1 Hz); LRMS (ESI) 344 [(M+H)]⁺.

Preparation 3

(\pm)-*cis*-1-Benzoyl-4-isopropyl-3-triethylsilyloxy-azetidin-2-one

25



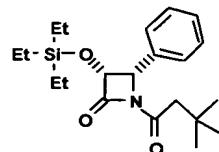
A solution of (+)-*cis*-4-isopropyl-3-triethylsilyloxy-azetidin-2-one (486 mg, 2.00 mmole), benzoyl chloride (0.255 mL, 1.1 equiv), diisopropylethyl amine (0.346 mL, 30 1.2 equiv) and p-dimethylaminopyridine (244 mg, 1 equiv) in dry DCM (6 mL) was

left stirring at 0 °C for 6 hr. The bath was removed and the reaction was left stirring overnight. It was then diluted with DCM and washed with water, aq. HCl solution (0.1 N), saturated aq. NaHCO₃ solution, brine and dried (Na₂SO₄). Removal of the solvent followed by silica gel column chromatography (gradient elution with 0 to 5% EtOAc in hexane) gave the title compound: ¹H NMR δ (CDCl₃) 0.47 - 0.94 (m, 21H), 2.09 (m, 1H), 4.07 (m, 1H), 4.75 (m, 1H), 7.24 - 7.76 (m, 5H).

Preparation 4

(3R,4R)-1-Neopentylcarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one

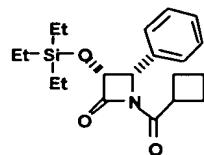
10



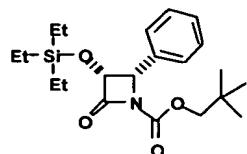
By following the above procedure and using neopentylcarbonyl chloride, and (3R,4R)-4-phenyl-3-triethylsilyloxy-azetidin-2-one were converted to the title product: ¹H NMR (CDCl₃) δ 0.19 - 0.62 (m, 15H), 0.88 (s, 3H), 2.43 (d, 1H, J = 13.8 Hz), 2.62 (d, 1H, J = 14.1 Hz), 4.90 (d, 1H, J = 5.7 Hz), 4.95 (d, 1H, J = 6.0 Hz), 7.05 - 7.17 (m, 5H).

Preparation 5

(3R,4R)-1-Cyclobutylcarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one



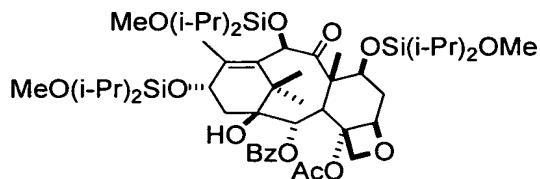
By following the above procedure and using cyclobutylcarbonyl chloride, (3R,4R)-4-phenyl-3-triethylsilyloxy-azetidin-2-one was converted to the title product: ¹H NMR (CDCl₃) δ 0.18 - 0.61 (m, 15H), 1.66 - 2.22 (m, 6H), 3.61 (m, 1H), 4.89 (d, 1H, J = 5.7 Hz), 4.94 (d, 1H, J = 5.7 Hz), 7.03 - 7.18 (m, 5H).

Preparation 6**(3R,4R)-1-Neopentyloxycarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one**

5

By following the above procedure and using neopentylchloroformate, (3R,4R)-4-phenyl-3-triethylsilyloxy-azetidin-2-one was converted to the title product: ^1H NMR (CDCl_3) δ 0.39 - 0.97 (m, 24H), 3.73 (d, 1H, J = 10.2 Hz), 3.90 (d, 1H, J = 10.2 Hz), 5.10 (m, 2H), 7.31 (m, 5H).

10

Preparation 7**1) Synthesis of baccatin derivative 1**

15

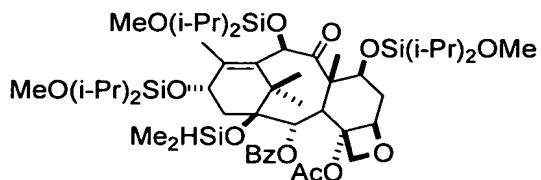
To a solution of 10-desacetyl baccatin (47.4 g, 87 mmol) in anhydrous N,N-dimethylformamide (DMF) (500 mL) was added imidazole (47g, 691 mmol) at ambient temperature. Solution was stirred for 10-15 min until a clear solution was observed. Dropwise, diisopropyl dichlorosilane (58 mL, 322 mmol) was added to the reaction mixture. Reaction mixture was stirred for 16 h at ambient temperature. Additional amount of diisopropyl dichlorosilane (6 mL) was added to the solution and the reaction was stirred for 60 min. HPLC at this point indicated completion of the reaction. Methanol (36 mL) was added to the mixture and the solution was stirred for 60 min. Reaction was stopped and diluted with a mixture of *tert*-butyl methyl ketone (TBME) (500 mL) and water (200 mL). Layers were separated and organic phase was washed with brine (250 mL), dried (sodium sulfate) and evaporated to afford the

trisilylated baccatin derivative **1**, (91 g, >100% yield) as a white amorphous compound which was used in the next step without further purification.

ESILRMS M+ calcd. For C₅₀H₈₄O₁₃Si₃: 977. Found 977

5

2) Synthesis of baccatin derivative 2

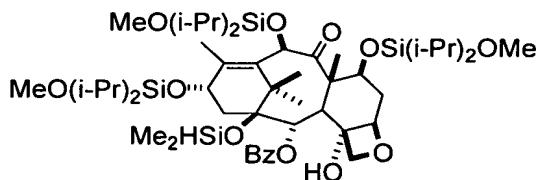


10 To a solution of baccatin derivative **1** (90 g, 92 mmol) in DMF (500 mL) was added imidazole (22 g, 320 mmol) at 0 °C. Dimethylchlorosilane (35 mL, 320 mmol) was added dropwise at 0 °C. Precipitation of the compound was observed at this point. Reaction mixture (slurry) was stirred for 0.5 h at 0 °C. Solid was filtered and washed with cold DMF (3X150 mL). After air drying, solid was redissolved in
15 TBME (700 mL) and the solution was washed with water (3 X 200 mL), brine (250 mL) and dried (sodium sulfate). The solution was filtered through a short silica pad. Removal of the solvent under vacuum afforded **2** in 77% yield (70 g).

ESILRMS M+ calcd. For C₅₀H₉₀O₁₃Si₄: 1035. Found 1035

20

3) Synthesis of baccatin derivative 3



25 To a stirred solution of **2** (66.3 g, 64 mmol) in toluene (680 mL) at -34 °C was added Red-Al (50 mL, 160 mmol, 65 wt% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene) dropwise over a period of 10 min.

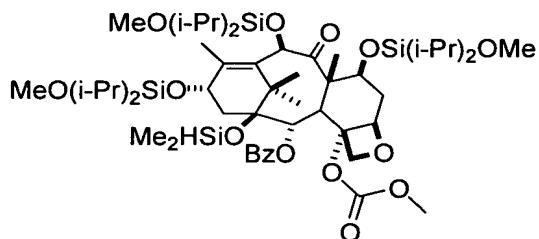
Reaction mixture was warmed to -25 °C and stirred for 1.5 h. Methanol (62 mL) was added dropwise to the reaction mixture keeping internal temperature between -20 and -25 °C. Solution was diluted with TBME (500 mL) followed by the addition of 1N sodium hydroxide solution (60 mL) and brine (60 mL). Solution was stirred for 30 min. Celite (12 g) was added to the mixture, stirred for 10 min, and filtered through a pad of celite. Layers were separated. Organic layer was washed with water, brine, and dried (sodium sulfate). Next, solution was passed through a short silica pad before removal of the solvent. The compound was obtained in 97% yield (62 g) as a white solid.

10

ESILRMS M+ calcd. For $C_{50}H_{88}O_{12}Si_4$: 993. Found 993

4) Synthesis of baccatin derivative 4

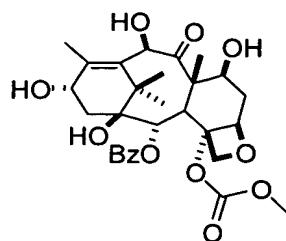
15



Under argon atmosphere, to a solution of **3** (62 g, 62 mmol) in anhydrous tetrahydrofuran (THF) (600 mL) at -60 °C was added LHMDS (lithium bis(trimethylsilyl)amide (125 mL, 125 mmol, 1M solution in THF) dropwise.

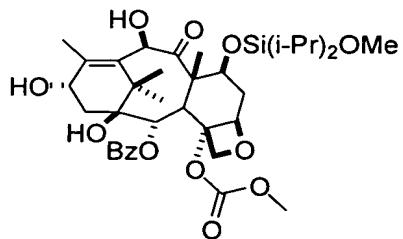
20 Solution was stirred for 15 min followed by the addition of methyl chloroformate (9 mL, 116 mmol); internal temperature of the solution was maintained at -60 °C. Reaction was slowly warmed to 0 °C and mixture was stirred for 3 h. After completion of the reaction, saturated ammonium chloride (300 mL) was added. Reaction mixture was extracted with TBME (100 mL). Organic layer was washed with saturated ammonium chloride (200 mL), water (200 mL), brine (200 mL), dried (sodium sulfate), and evaporated to provide **4** as an oil (67 g, >100%). The crude material was used in the next step without further purification.

25 ESILRMS M+ calcd. For $C_{52}H_{90}O_{14}Si_4$: 1051. Found 1051.

5) Synthesis of baccatin derivative 5

5 To a solution of baccatin derivative 4 (62 g, 59 mmol) in dry THF (260 mL) was added triethylamine•hydrofluoric acid complex (56 mL, 344 mmol) at ambient temperature. Reaction was stirred for 3 h. Reaction mixture was diluted with ethyl acetate (350 mL) and washed with water (200 mL), brine (200 mL), dried (sodium sulfate), and evaporated to afford 5 (43 g, >100% crude yield). Resluring of the crude
10 compound in a mixture of hot ethylm acetate (350 mL) and hexanes (50 mL) gave pure 5 in 90% yield.

ESILRMS M+ calcd. For $C_{29}H_{36}O_{11}$: 560. Found 560.

15 6) Synthesis of baccatin derivative 6

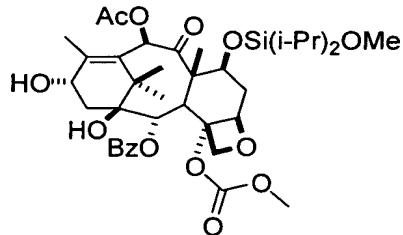
20 To a stirred solution of baccatin 5 (32 g, 57 mmol) and imidazole (11.7, 172 mmol in DMF (220 mL) at -65 °C was added diisopropylchlorosilane (26.8 mL) under argon. Temperature of the reaction mixture was maintained at -60 °C and the mixture was stirred for 2 h. After completion of the reaction (HPLC), a solution of imidazole in methanol (11.7 g imidazole dissolved in 35 mL methanol) was added and the solution was stirred at 0 °C for 30 min. Mixture was extracted with TBME (500 mL). Organic phase was washed with water (4x150 mL), dried (sodium sulfate), and

evaporated to afford crude **6** (45 g). The crude material was further dissolved in acetonitrile (150 mL) and the solution was washed with hexanes (3X100 mL). Removal of acetonitrile afforded pure **6** as a white solid (34 g, 84% yield).

5 ESILRMS M+ calcd. For $C_{36}H_{52}O_{12}Si$: 704. Found 704.

7) Synthesis of baccatin derivative 7

4-deacetyl-7-[bis(isopropyl(methoxy)silyloxy]-4-methoxycarbonyl-baccatin



10

To a solution of baccatin derivative **6** (33.2 g, 47 mmol) in DMF (200 mL) was added LHMDS (61.2 mL, 61.2 mmol) dropwise at -43 °C. Reaction was stirred for 15 min followed by the addition of acetic anhydride (5.8 mL, 63 mmol). Reaction was stirred for 30 min. at -40 °C. Acetic acid (3.6 mL) was added and the cooling bath was removed. Reaction mixture was extracted with TBME (300 mL). Organic layer was separated and washed with water (3x150 mL), brine (150 mL), dried (sodium sulfate), and evaporated to afford the crude product. Purification of this compound was achieved by crystallization from a mixture of THF:heptane (1:6). Input of 40 g provided 21 g of crystallized baccatin derivative **7** (60% yield).

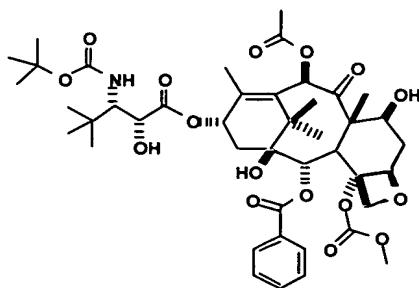
15
20

ESILRMS M+ calcd. For $C_{38}H_{54}O_{13}Si$: 746. Found 746.

25

Example 1 Compound Ia

**3'-*tert*-Butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-
5 4-O-methoxycarbonyl-paclitaxel**



A solution of (+)-cis-4-*tert*-butyl-1-(*tert*-butyloxycarbonyl)-3-triethylsilyloxy-
10 azetidin-2-one (2.71 gm, 5 equiv) and 4-deacetyl-7-[bis(isopropyl(methoxy)silyloxy]-
4-methoxycarbonyl-baccatin (1.13 gm, 1.52 mmole) in dry THF (100 mL) under N₂
was cooled to -50 °C and a solution of LiHMDS (1.97 mL, 1.3 equiv, 1.0 M in
THF) was added. After 5 min this was transferred to a bath that was maintained at -35
to -30 °C for 20 hr and then -25 °C for 24 hr. The reaction was then quenched with
15 saturated aqueous NH₄Cl solution and extracted with a mixture of EtOAc and hexane
(1:1). The organic extracts were washed with brine and dried (Na₂SO₄). The
solvents were removed and the residue was chromatographed (radial chromatography
on a 6 mm silica gel plate; gradient elution with 5 to 20% EtOAc in hexane) to afford
1.55 gm of 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-7-
20 [bis(isopropyl(methoxy)silyloxy]-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-
methoxycarbonyl-2'-triethylsilyloxy paclitaxel as a mixture of 2', 3'-diastereomers.
This mixture was dissolved in dry THF (60 mL) and triethylamine trihydrofluoride
(0.92 mL 4 equiv) were added. After 22 hr at RT, the reaction was neutralized with
25 saturated aq. NaHCO₃ solution and then extracted with EtOAc. The organic extracts
were washed with brine, dried (Na₂SO₄) and the solvents were removed. The residue
was chromatographed (radial chromatography; 2 mm silica gel plate; gradient elution
from 10 to 50% EtOAc in hexane) to afford (in order of elution): 210 mg (18%) of

2'S,3'R-3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel {¹H NMR (CDCl₃) δ 1.04 (s, 9H), 1.13 (s, 3H), 1.20 (s, 3H), 1.37 (s, 9H), 1.65 (s, 1H), 1.66 (s, 3H), 1.84 - 1.93 (m, 2H), 2.17 (s, 3H), 2.25 (s, 3H), 2.55 (m, 3H), 3.00 (d, 1H, J = 6.5 Hz), 3.74 (d, 1H, J = 10.8 Hz), 5 3.79 (d, 1H, J = 6.9 Hz), 3.92 (s, 3H), 4.16 (d, 1H, J = 8.5 Hz), 4.33 (d, 1H, J = 8.5 Hz), 4.42 (m, 1H), 4.54 (d, 1H, J = 6.5 Hz) 4.87 (d, 1H, J = 10.6 Hz), 5.01 (d, 1H, J = 7.7 Hz), 5.68 (d, 1H, J = 7.0 Hz), 5.76 (m, 1H), 6.32 (s, 1H), 7.44 - 8.05 (m, 5H); LRMS (ESI) 846 [(M+H)⁺] and 668 mg (56%) of the title compound {¹H NMR (CDCl₃) δ 1.07 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.33 (s, 9H), 1.66 (s, 4H), 2.23 (s, 10 3H), 2.38 - 2.59 (m, 4H), 3.11 (d, 1H, J = 5.8 Hz), 3.77 (d, 1H, J = 11.1 Hz), 3.82 (d, 1H, J = 7.0 Hz), 3.96 (s, 3H), 4.20 (d, 1H, J = 8.6 Hz), 4.33 (d, 1H, J = 8.6 Hz), 4.39 (m, 1H), 4.53 (d, 1H, J = 5.4 Hz) 4.88 (d, 1H, J = 10.6 Hz), 4.98 (d, 1H, J = 7.9 Hz), 5.69 (d, 1H, J = 7.1 Hz), 6.03 (m, 1H), 6.28 (s, 1H), 7.40 - 8.11 (m, 5H); LRMS (ESI) 846 [(M+H)⁺]}.
15

Example 2 Compound Ib

3'-N-*tert*-Butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-3'-isopropyl-4-O-methoxycarbonyl-paclitaxel

By following the above procedure, (\pm)-*cis*-1-*tert*-butyloxycarbonyl-4-isopropyl-3-triethylsilyloxy-azetidin-2-one was coupled with 4-deacetyl-7-[bis(isopropyl(methoxy)silyloxy]-4-O-methoxycarbonyl-baccatin. Deprotection followed by chromatography gave the title compound ¹H NMR (CDCl₃ + D₂O) δ 1.03 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz), 1.14 (s, 3H), 1.24 (s, 3H), 1.31 (s, 9H), 1.66 (m, 3H), 1.83 - 2.02 (m, 5H), 2.24 (s, 3H), 2.25 - 2.59 (m, 3H), 3.68 (dd, 1H, J = 2.0, 9.2 Hz), 3.82 (d, 1H, J = 6.9 Hz), 3.98 (s, 3H), 4.19 (d, 1H, J = 8.6 Hz), 4.34 (d, 1H, J = 8.6 Hz), 4.39 (m, 1H), 4.43 (d, 1H, J = 2.0 Hz) 4.82 (br s, 1H), 4.98 (d, 1H, J = 7.8 Hz), 5.69 (d, 1H, J = 7.0 Hz), 6.11 (m, 1H), 6.28 (s, 1H), 7.45 - 8.12 (m, 5H); LRMS (ESI) 832 [(M+H)⁺].
20
25

Example 3 Compound Ic**3'-N-Neopentylcarbonyl-4-deacetyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel:**

A solution of (3R,4R)-1-neopentylcarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one (525 mg, 1.4 equiv) and 4-deacetyl-7-[bis(isopropyl(methoxy)silyloxy)-4-O-methoxycarbonyl-baccatin (523 mg, 0.700 mmole) in dry THF (15 mL) was cooled to -50 °C and a solution of LiHMDS (0.84 mL, 1.2 equiv, 1.0 M in THF) was added with stirring. After 40 min, the reaction was allowed to warm to 0 °C. After 1.5 hr, this was quenched with a saturated aq. solution of NH₄Cl, the reaction was extracted with EtOAc. The organic extract was washed with a saturated aq. solution of NH₄Cl, water, brine and dried (Na₂SO₄). Removal of the solvents followed by silica gel column chromatography (gradient elution with mixtures of 0% to 20% EtOAc in hexane) afforded 2.78 mg (54%) of 3'-N-neopentyloxycarbonyl-7-[bis(isopropyl(methoxy)silyloxy)-4-deacetyl-3'-N-debenzoyl-4-O-methoxycarbonyl-2'-triethylsilyloxy-paclitaxel. This was taken directly and treated with triethylamine trihydrofluoride (0.161 mL, 4 equiv) in dry THF (6 mL) and left stirring at RT overnight. After neutralization with saturated aq. NaHCO₃ solution, the reaction was extracted with EtOAc. The organic extracts were washed with brine and dried (Na₂SO₄). Removal of the solvents followed by silica gel column chromatography (gradient elution with mixtures of 20 to 50% EtOAc in hexane) afforded 151 mg (71%) of the title product: ¹H NMR (CDCl₃) δ 0.96 - 2.58 [32H, including 0.96 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.66 (s, 3H), 1.84 (s, 3H), 2.23 (s, 3H)], 3.58 (br s, 1H), 3.77 (s, 3H), 3.80 (d, 1H, J = 5.5 Hz), 4.19 (d, 1H, J = 8.3 Hz), 4.33 (d, 1H, J = 8.7 Hz), 4.36 (m, 1H), 4.65 (d, 1H, J = 2.0 Hz), 4.95 (d, 1H, J = 8.5 Hz), 5.58 (dd, 1H, J = 2.3, 8.8 Hz), 5.69 (d, 1H, J = 7.0 Hz), 6.11 (d, 1H, J = 8.9 Hz), 6.16 (m, 1H), 6.27 (s, 1H), 7.29 - 8.12 (m, 10H); LRMS (ESI) 864 [(M+H)⁺].

Example 4 Compound Id**3'-N-Cyclobutyl-4-deacetyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel:**

By following the above procedure and using (3R,4R)-1-cyclobutyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one, 4-deacetyl-7-[bis(isopropyl(methoxy)silyloxy]-4-O-methoxycarbonyl-baccatin was converted to the title product: ^1H NMR (CDCl_3) δ 1.14 - 2.53 [m, 27H including: 1.14 (s, 3H), 1.25 (s, 3H), 1.67 (s, 3H), 1.84 (s, 3H), 2.24 (s, 3H)], 3.01 (m, 1H), 3.56 (br s, 1H), 3.81 (s, 3H), 3.82 (m, 1H), 4.20 (d, 1H, $J = 8.4$ Hz), 4.34 (d, 1H, $J = 8.5$ Hz), 4.37 (m, 1H), 4.68 (d, 1H, $J = 2.3$ Hz), 4.96 (d, 1H, $J = 8.6$ Hz), 5.58 (dd, 1H, $J = 2.4, 9.0$ Hz), 5.70 (d, 1H, $J = 7.0$ Hz), 6.16 (m, 2H), 10 6.27 (s, 1H), 7.29 - 8.14 (m, 10H); LRMS (ESI) 848 [(M+H) $^+$].

Example 5 Compound Ie**3'-*tert*-Butyl-3'-N-cyclohexyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel**

15 By following the same procedure with cyclohexyloxymchloroformate, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel was converted to the title product: ^1H NMR ($\text{CDCl}_3 + \text{D}_2\text{O}$) δ 1.10 - 2.61 [38H, including 1.10 (s, 9H), 1.16 (s, 3H), 1.26 (s, 3H), 1.69 (s, 3H), 1.95 (s, 3H), 2.26 (s, 3H)], 3.84 (m, 2H), 3.99 (s, 3H), 4.23 (d, 1H, $J = 8.6$ Hz), 15 4.40 (m, 3H), 4.57 (s, 1H), 5.02 (m, 2H), 5.7 (d, 1H, $J = 7.08$ Hz), 6.06 (m, 1H), 6.30 (s, 1H), 7.46 - 8.13 (m, 5H); LRMS (ESI) 872 [(M+H) $^+$].

Example 6 Compound If**3'-*tert*-Butyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-3'-N-neopentylcarbonyl-4-****O-methoxycarbonyl-paclitaxel**

By following the above procedure with *tert*-butylacetil chloride, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel was converted to the title product ^1H NMR ($\text{CDCl}_3 + \text{D}_2\text{O}$) δ 1.00 - 2.56 [39H, including 1.00 (s, 9H), 1.11 (s, 9H), 1.16 (s, 3H), 1.26 (s, 3H), 1.69 (s, 3H), 1.91 (s, 3H), 2.26 (s, 3H)], 3.83 (d, 1H, $J = 7.1$ Hz), 3.98 (s, 3H), 4.17 (d, 1H, $J = 10.1$ Hz), 30

4.26 (d, 1H, J = 8.8 Hz), 4.37 (m, 2H), 4.55 (s, 1H), 5.00 (d, 1H, J = 7.5 Hz), 5.73 (m, 2H), 6.02 (m, 1H), 6.29 (s, 1H), 7.45 - 8.13 (m, 5H); LRMS (ESI) 844 [(M+H)⁺].

Example 7 Compound Ig

- 5 **4-deacetyl-3'-N-debenzoyl-3'-N-tertbutoxycarbonyl-4-O-methoxycarbonyl-paclitaxel**

By following the above procedures and using (3R,4R)-1-tertbutoxycarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one, compound Ig was prepared.

- 10 ¹H NMR (300 MHz, CDCl₃): δ 8.13-8.10 (m, 2H), 7.61-7.26 (m, 8H), 6.27 (s, 1H), 6.19 (m, 1H), 5.68 (d, J=6.9Hz, 1H), 5.35-5.29 (m, 2H), 4.97 (d, J=7.7Hz, 1H), 4.63 (d, J=3.9Hz, 1H), 4.42-4.37 (m, 1H), 4.25 (AB q, J=8.8Hz, J=47.7Hz, 2H), 3.85-3.81 (m, 4H), 3.40 (d, J=5.1Hz, 1H), 2.59-1.03 (m, 30H, include singlets at 2.24, 1.87, 1.71, 1.27, 1.14, 3H each, 1.32, 9H).

- 15 **Example 8 Compound Ih**

4-deacetyl-3'-N-debenzoyl-3'-N-nbutoxycarbonyl-4-O-methoxycarbonyl-paclitaxel

Using the procedures described above with (3R,4R)-1-nbutoxycarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one, compound Ih was prepared.

- 20

¹H NMR (300 MHz, CDCl₃): δ 8.11 (d,J=7.4Hz,2H), 7.62-7.29 (m, 10H), 6.27 (s,1H), 6.27 (m,1H), 5.69 (d, J=7.0Hz,1H), 5.41 (abq, J=47.4,9.4 Hz, 2H), 4.97 (d, J=7.0Hz, 1H), 4.66 (brs, 1H), 4.38-4.32 (m,1H), 4.26 (abq, 45.0, 8.6Hz, 2H), 3.83 (s,3H), 3.42 (brd, J=4.1Hz,1H), 2.59-2.35 (m,4H), 2.24 (m,3H), 1.86 (s,3H), 1.67 (s,3H), 1.65 (d, J=33.0Hz, 3H), 1.67 (s,3H), 1.51-1.47 (m,2H), 1.24 (s, 3H), 1.14 (s,3H), 0.83 (m,3H).

Anal. calcd. for C₄₅H₅₅NO₁₆: C,62.42; H,6.40; N,1.62. Found: C, 62.28; H, 6.45; N, 1.55.

Example 9 Compound Ij**3'-*N*-debenzoyl-3'-*N*-cyclobutylcarbonyl-3'-dephenyl-3'-*tert*-butyl-4-deacetyl-4-methoxycarbonyl paclitaxel**

A solution of 3'-*N*-debenzoyl-3'-*N*-*tert*-butyl-3'-dephenyl-3'-*tert*-butyl-4-deacetyl-4-methoxycarbonyl paclitaxel (2.30 g, 2.72 mmoles) in DCM (15.0 mL) was treated with trifluoroacetic acid (15.0 mL) and stirred at 0°C for 1.5 hrs. The mixture was diluted with 100 mL DCM and poured into a cold solution (0°C) made up of 50.0 g NaHCO₃ in 150 mL water. The phases were separated and the organic layer was concentrated *in vacuo*. The product could be purified by column chromatography on silica gel eluting with 4% methanol/DCM, but was generally used without purification. The crude 3'-*N*-debenzoyl-3'-dephenyl-3'-*tert*-butyl-4-deacetyl-4-methoxycarbonyl paclitaxel was dissolved in ethyl acetate (15.0 mL) and treated with saturated NaHCO₃ (15.0 mL). Cyclobutane carbonyl chloride (460.0 μL, 4.08 mmoles, 1.5 equiv.) was added and the biphasic mixture was stirred vigorously at ambient temperature for 20 mins. The mixture was diluted with ethyl acetate, and the phases were separated. The organic phase was washed with saturated NaHCO₃, then brine. The organic solution was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Purification by preparative reverse phase chromatography eluting with 20% acetonitrile/water for 5 mins. ramping up to 60% acetonitrile/water over 45 mins, then isocratic for 45 mins. at a flow rate of 250 mL/min. afforded the title compound (1.47g, 65% yield, 97% pure by HPLC analysis) as a white, amorphous solid which exhibited the following physical properties: ¹H NMR (CDCl₃, 300 MHz) δ 8.08 (d, J = 7.1 Hz, 2H), 7.62–7.55 (m, 1H), 7.48–7.43 (m, 2H), 6.27 (s, 1H), 5.99 (dd, J = 7.8 Hz, J = 9.0 Hz, 1H), 5.69 (m, 2H), 4.98 (dd, J = 2.0 Hz, J = 9.5 Hz, 1H), 4.55 (dd, J = 1.1 Hz, J = 5.2 Hz, 1H), 4.40–4.32 (bm, 2H), 4.22 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 10.2 Hz, 1H), 3.98 (s, 3H), 3.80 (d, J = 7.0 Hz, 1H), 3.30 (d, J = 5.1 Hz, 1H), 2.97 (p, J = 7.9 Hz, 1H), 2.58–2.36 (bm, 4H), 2.23 (s, 3H), 2.19–2.03 (bm, 4H), 1.92–1.76 (bm, 3H), 1.88 (s, 3H), 1.66 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.06 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 203.70, 174.99, 174.93, 171.46, 166.89, 153.21, 142.54, 133.74, 133.20, 130.22, 129.81, 128.72, 84.13, 83.21, 78.92, 76.09, 75.68, 74.94, 73.39, 72.06, 70.17, 58.36, 57.73, 56.03, 51.07, 45.74, 43.34,

39.91, 35.94, 35.47, 27.37, 26.85, 25.60, 25.44, 22.12, 20.95, 18.29, 14.95, 9.72; LRMS (ESI): 828.51 ((M+1)⁺, 100%), 886.57 ((M+NH₄+ACN)⁺, 15%); 826.48 ((M-1)⁻, 100%).

5 **Example 10 Compound Ik**

3'-N-debenzoyl-3'-N-(2-furoyl)-3'-dephenyl-3'-*tert*-butyl-4-deacetyl-4-methoxycarbonyl paclitaxel

Prepared similarly to Example 9 above. The title compound (2.13 g, 73% yield, 98% pure by HPLC analysis) was obtained as a white, amorphous solid which exhibited the following physical properties: ¹H NMR (CDCl₃, 300 MHz) δ 8.15–8.08 (m, 2H), 7.64–7.56 (m, 1H), 7.52–7.25 (m, 3H), 7.03 (dd, J = 0.6 Hz, J = 3.4 Hz, 1H), 6.78 (d, J = 10.2 Hz, 1H), 6.48 (dd, J = 1.8 Hz, J = 3.5 Hz, 1H), 6.25 (s, 1H), 6.06 (dd, J = 7.6 Hz, J = 8.9 Hz, 1H), 5.70 (d, J = 7.0 Hz, 1H), 5.00 (dd, J = 1.9 Hz, J = 9.4 Hz, 1H), 4.40–4.32 (m, 3H), 4.23 (d, J = 8.6 Hz, 1H), 4.05 (s, 3H), 3.48 (d, J = 4.5 Hz, 1H), 2.60–2.50 (m, 2H), 2.38 (dd, J = 3.3 Hz, J = 8.8 Hz, 1H), 2.23 (s, 3H), 2.05 (s, 1H), 1.95–1.85 (m, 1H), 1.81 (s, 3H), 1.68 (s, 3H), 1.21 (s, 3H), 1.14 (s, 12H); ¹³C NMR (CDCl₃, 75 MHz) δ 203.71, 174.23, 171.55, 167.06, 158.22, 153.06, 147.65, 144.30, 142.53, 133.93, 133.36, 130.32, 129.42, 128.88, 114.95, 112.51, 84.20, 83.48, 79.06, 77.65, 76.20, 75.81, 75.05, 72.96, 70.55, 58.50, 57.97, 56.40, 46.07, 43.33, 36.09, 35.55, 27.53, 27.05, 22.00, 21.25, 21.06, 14.97, 14.39, 9.83; LRMS (ESI): 840.43 ((M+1)⁺, 100%); 838.43 ((M-1)⁻, 100%).

Biological Data

Another aspect of the instant invention concerns a method for inhibiting 25 human and/or other mammalian tumors which comprises orally administering to a tumor bearing host an antitumor effective amount of a compound of formula I.

The materials and methods utilized for the in vivo antitumor testing of our oral taxanes are summarized below:

Materials

Animals. Conventional or athymic ("nude") mice, and nude rats, were implanted subcutaneously (sc) with tumor brei or fragments. Murine tumor were implanted in conventional mice, human tumors were implanted into nude mice or rats.

5

Tumors. The tumors utilized most often included the murine lung carcinoma, M109, the murine mammary carcinoma, MAM 16/C, the human ovarian carcinoma, A2780, the human colon tumors, HCT-116 and HCT-116/pk. Compounds I exhibited antitumor activity after oral administration in one or more of the aforementioned tumor models.

10

Methods for the Table III Results

The experiments were carried out using athymic ("nude") mice. Typically, treatments were begun when tumors were between 100 and 500 mg in size (typically Day 7 to

15

Day 12 post-tumor implant) for the A2780 human ovarian tumor xenograft model.

Group sizes were typically 8 per treatment and control groups in mouse experiments. The compound was administered at the dose indicated in Table III, namely, once daily every other day for five treatments (i.e. q2dx5).

20

Treatments for taxanes administered orally (po) were done by gavage using a vehicle consisting of 10% ethanol + 10% Cremophor EL + 80% water. The volume of liquid administered was 0.01 ml per gram of body weight for mice. A typical mouse experiment would involve the evaluation of each test compound at three different dose levels.

25

Antitumor activity was assessed by determining the size of tumors in all treated and control experimental animals over time. Each animal was individually identified and the growth of the tumor implanted into each animal was measured once or twice weekly using a calipers. The difference in median time for tumors in treated (T) and

30

control (C) groups to reach a predetermined size (e.g., 500 or 1,000 milligrams) was calculated, and assessments of absolute and relative antitumor effects (e.g., between compounds) were made on the basis of the delays in time to reach predetermined

tumor target sizes. Animals with tumors of 35 mg or less at the termination of an experiment were termed "cures". Experiments were terminated typically after a period of time had elapsed post-treatment that was at least 10 times the tumor volume doubling time (TVDT) of the median tumor growth in control animals as assessed 5 prior to their reaching the predetermined tumor target size in each experiment.

Activity in a test group was defined as having caused a delay in tumor growth (median time to reach tumor target size) relative to the concomitant control tumor growth (i.e., T-C) of 3.32 times the TVDT. Activity was expressed in "log cell kill" which was equal to (T-C)/ (TVDT x 3.32). Toxicity was determined by measuring the average 10 body weight of all animals in an experiment prior to, and soon after, any treatments in the experiment. Additionally, animals were considered to have died due to treatment - induced injury if they died prior to any deaths in the control group with tumors smaller than target size. No results of therapy, nor any declaration of activity, was used or made for a particular treatment group if more than one animal in that group died in a 15 manner characterized as treatment-induced.

All of the compounds in Table III displayed oral antitumor activity in a ScM109 tumor model implanted in mice which was judged to be equivalent to the antitumor activity of paclitaxel administered intravenously according to its optimum schedule of administration and dose.

20

Table III
In Vivo Activity vs Sc A2780 of
Orally Active C-4 Methyl Carbonate Taxanes

Compound	Oral Dose ^a	Schedule	Oral Efficacy vs. Sc A2780 Log Cell Kill ^c (Cures/Treated) ^b
Ia	65	q2dx5	4.4 (0/8)
Ib	28	q2dx5	3.0 (1/8)**
Ic	100	q2dx5	3.8 (0/8)
Id	140	q2dx5	4.1 (0/8)
Ie	55	q2dx5	1.5 (0/8)
If	36	q2dx5	1.8 (0/8)

Ig	32	q2dx5	0.9 (0/8)
Ih	100	q2dx5	7.0 (1/8)**
Ij	120	q2dx5	2.1 (0/8)
Ik	130	q2dx5	2.2 (0/8)

a. Optimal or maximum tolerated dose level tested in milligrams per kilogram. The dose given is for a single administration and is repeated for each of the five administrations. The total amount of compound given for the complete course of treatment is therefore five times the oral dose indicated in Table III.

5 ** One of eight tested mice was cured

b. The number of mice judged to be cures (as defined above) divided by the total number of treated mice is the meaning for "cures/treated," which appears in 10 parenthesis in Table III.

c. "Log Cell Kill" has already been defined above.

As can be seen from the results of Table III, all the compounds Ia-Ik displayed 15 significant oral antitumor activity. Significant antitumor activity is defined as being approximately one log cell kill. This can be contrasted with results that would be observed for compounds which would have no oral activity, such as paclitaxel (i.e. having approximately zero log cell kill). It should be recognized that paclitaxel, which is the active ingredient of the commercially available anticancer drug, 20 TAXOL®, is administered intravenously and is not used in oral administration since it is not effective.

For treating a variety of tumors, the compound of formula I of the present invention may be used in a manner similar to that of paclitaxel, e.g. see Physician's Desk Reference, 49th Edition, Medical Economics, p 682, 1995. The dosage, 25 mode and schedule of administration for the compound of this invention are not particularly restricted; an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering the compound of the present invention. Thus the

compound of formula I may be administered via any suitable route of administration, parenterally or orally. Parenteral administration includes intravenous, intraperitoneal, intramuscular, and subcutaneous administration.

The doses utilized to implement the methods in accordance with the invention are the ones that make it possible to administer prophylactic treatment or to evoke a maximal therapeutic response. The doses vary, depending on the type of administration, the particular product selected, and the personal characteristics of the subject to be treated. In general, the doses are the ones that are therapeutically effective for the treatment of disorders caused by abnormal cell proliferation. The products in accordance with the invention can be administered as often as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require mild maintenance or no maintenance dose at all. Via the iv route, the dosage may be, for example, in the range of about 20 to about 500 mg/m² over 1 to 100 hours.

Via the oral route, the dosage may be in the range of 5-1000mg/kg/day of body weight. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient.

The present invention also provides pharmaceutical formulations (compositions) containing an antitumor effective amount of compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. The compositions can be prepared in accordance with conventional methods. Examples of formulating paclitaxel or derivatives thereof may be found in, for example, United States Patents Nos. 4,960,790 and 4,814,470, and such examples may be followed to formulate the compound of this invention. Additional examples of paclitaxel formulations are found in the general references cited earlier in the background art. For example, compound of formula I may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. It may also be manufactured in the form of sterile solid compositions, for example, freeze dried and, if desired, combined

with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use for parenteral administration.

- 5 Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical
10 preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.